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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/702,232	EGLEN, RICHARD M.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/6/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending in the application.

Priority

This application repeats a substantial portion of prior Application No. 10/292,747, filed 8/27/02, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Specifically US application 10/229,747, as well as provisional applications 60/316,248 and 60/353086, lacks disclosure of a method drawn to analyzing the effect of inhibition of expression by an expression inhibiting nucleic acid. US application 10/229,747 is drawn to a method of assaying the status of a cell by use of alpha-complementation. While 10/229,747 contemplates the use of antisense DNA or RNAi, the purpose of these molecules is to generate cells lines in which endogenous genes are removed (see e.g. paragraph 0066). However, US 10.229,747 does not contemplate use of these molecules to target the fusion peptide comprising ED. These teachings have been added to the instant specification at the following places: bridging paragraphs page 2-3, paragraph 0037 and the instant claims. Therefore, the priority date of the instant application is its filing date, 11/6/03.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the address of Richard M Elgen has been altered.

Specification

The abstract of the disclosure is objected to because RNA*i* is abbreviated and must be spelled out for clarity. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 1 is objected to because of the following informalities: For clarity, in line 2, a comma is required between the phrase "interacts with mRNA' and the word "using". Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of "analyzing in a cell for the effect" are unclear. It is unclear how you can analyze "for" an effect. If the claim intends to recite, "analyzing the effect of an expression inhibiting nucleic acid", the claim lacks any methods steps that would lead to an analysis of the effect of the expression inhibiting nucleic acid. Rather the method leads to a detection or lack of detection of an effect of the inhibitor on expression.

Claims 1 and 8 are vague and indefinite in that the metes and bounds of "a fusion protein of the small enzyme donor fragment of β-galactosidase with a polypeptide" are unclear. By stating that the construct expresses a fusion protein "of" ED "with a polypeptide" it is not clear if the fusion protein comprises ED and a second polypeptide or if the polypeptide is concomitantly used with the fusion protein.

Claims 1 and 8 are vague and indefinite in that the metes and bounds of "affects the activity of β-galactosidase" are unclear. As the preamble states that the nucleic acid interacts with mRNA, it is unclear how the nucleic acid affects the activity of the β-galactosidase resulting form an ED-EA complex. Claim 8 further states that the "activity of said ED in forming a functional enzyme" is effected. Therefore, it appears that the inhibitor blocks formation of a functional enzyme. However, by reciting that the "activity" is effected, the actual mechanism of activity of the inhibitor is unclear.

Claims 1 and 8 recite the limitation "providing said EA to any of said fusion protein produced in said cell" " in claim 1 or 8. There is insufficient antecedent basis for this limitation in the claim. It is not clear that there is more than on fusion protein produced.

Claims, 1, 8 and 13 are vague and indefinite in that the metes and bounds of "substrate produces a detectable product" are unclear. It is unclear how a substrate produces a product specifically a fluorescent product. The detectable product actually is the result of an enzymatic interaction of the substrate and a functional β-galactosidase. However, the claims appear to recite that the substrate produces a product.

Claims 6 and 15 are vague and indefinite in that the metes and bounds of "said cell is grown in the presence of a candidate compound" are unclear. Applicants simply state that "candidate compounds" are included in the methods. It is unclear what function the compounds are meant to perform if any. Furthermore, the qualitative nature of the compounds is unclear. Therefore, it is unclear what components are required to perform these method steps.

Claim 18 is vague and indefinite in that the metes and bounds of "a system" are unclear. Applicants do not provide a description of "a system" and therefore, it is unclear what constitutes "a system". While the claims recite that the system comprises constructs, it also recites measuring β-galactosidase activity. Is the system for determining the effect of expression of an inhibiting dsRNA, the vector expressing a fusion of ED, EA and a substrate, a method of determining the effect using the cell or a combination of the constructs and method steps? It is noted that if the term "system" encompasses both the constructs and methods of determining the effect using the constructs, use of the term in the instant claims directs the claim to non-statutory subject matter (i.e. methods and product claimed together in the same claim).

Claim 18 is vague and indefinite in that the metes and bounds of "a gene" in line 13 are unclear. It is unclear how a "gene" can express the inhibiting dsRNA as the dsRNA is said to be RNAi which is a short sequence of RNA that can be a portion of a gene.

Claim 18 recites the limitation "said first protein fusion protein" in claim 18. There is insufficient antecedent basis for this limitation in the claim.

Claim 18 is vague and indefinite in that the metes and bounds of "ED capable of complementing said EA" are unclear. It is unclear if a separate ED protein is provided to the cell or this is the same one recited in the step (2).

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 6-8, 11-16 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Thomas et al (US 6,727,070; see entire document).

Thomas et al teach use of an alpha complementation system using a specialized fusion protein and structural complementation (see e.g. abstract). As demonstrated in figure 1, a fusion protein is expressed comprising the alpha or small fragment of β-galactosidase (ED). Interaction of the alpha and omega or large fragment of β-galactosidase (EA) is detectable following addition of a substrate (see e.g. col 2, line 9-48). The target protein coding sequences were cloned into a vector comprising a promoter driving expression of ED followed by the cloning

site (see e.g. col 39, line 50- col 40, line 12). The fusion protein comprising the target protein and ED is expressed from a vector comprising a promoter that can be cell-type specific, inducible or constitutive. The particular promoter depends upon the cell type used (see e.g. table 1). The cells stably express EA (see e.g. col 42, line 3-5). Cells were also provided with modulators that effect protein folding and/or solubility. The modulators include antisense or ribozymes (see e.g. col 37, line 38-44). The fusions were inducibly expressed in the cell and to determine fluorescence, the cells were lysed and the lysate was used to determine activity such as by fluorescence (see e.g. paragraph col 38, line 29-39 and col 40, 45-64). The cells are grown in a variety of compounds such as neomycin, ampicillin or IPTG (see e.g. col 40, line 38-47). Mammalian cell lines are hosts for the method of Thomas et al (see e.g. paragraph col 22, line 24-32). The components of Thomas et al together would comprise a kit.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 4, 5, 9, 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al (2004/0241636 A1; see entire document) in view of Thomas et al (US 6,727,070; see entire document).

Applicants claim a method of analyzing the effect of an expression inhibiting nucleic acid using a cell comprising an expression construct expressing a fusion protein of ED and another polypeptide to which is provided EA. The expression inhibiting nucleic acid is a dsRNA or RNAi that can effect transcription factors.

Michnick et al teach a cell-based assay useful for mapping genes (proteins) into cellular pathways using fluorescence assays (see e.g. abstract). Cells are transfected with cDNAs encoding target proteins that are involved in signaling. The sequences are cloned into pCDNA3.1 which carries a CMV promoter for constitutive expression (see e.g. col 8, paragraph 0070-0071). The effect of compounds such as decoy DNAs, dsRNA or RNAi on signaling are assayed by targeting the signaling proteins as well as transcription factors (see e.g. figure 1, paragraph 0064 and table 1). The effects of the compounds identify dynamic modulations of proteins within pathways in living cells using high-throughput assays (see e.g. paragraph 0032). An example of high-throughput assays to analyze the effect of the inhibitory compounds is by alpha-complementation comprising the large and small subunit of β-galactosidase (see e.g. paragraph 0113). Interfering RNA for example is administered to the cell as purified RNA.

Michnick et al do not teach the actual components of the method of alpha-complementation.

The teachings of Thomas et al are as above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods steps for alpha-complementation as taught by Thomas et al to detect dynamic modulations of protein within pathways using alpha-complementation as taught by Michnick et al because Michnick et al teach that it is within the ordinary skill of the art to

assay the effects of RNAi using alpha-complementation and because Thomas et al teach that it is within the ordinary skill of the art to use a cell comprising a fusion of ED and the protein of interest and an expression inhibiting nucleic acid to which is provided EA to assay the effect of the expression inhibiting nucleic acid. A person of skill in the art would have been motivated to develop the alpha-complementation assay as described by Thomas et al encompassing the means described in Michnick et al due to the ease and success provided by Thomas et al to enable successful utilization of alpha-complementation. Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michnick et al (2004/0241636 A1; see entire document) in view of Thomas et al (US 6,727,070; see entire document) further in view of Allen et al (US 2004/0198967; see entire document).

Applicants claim a system comprising a vector comprising an ED sequence and a multiple cloning site into which is inserted a gene and the inhibiting dsRNA under the control of a transcriptional regulatory region and an EA and a substrate for β-galactosidase.

The teachings of Michnick et al and Thomas et al are as above except:

Neither Michnick et al or Thomas et al teach that the expression inhibiting nucleic acid is expressed using a transcriptional regulatory region.

Allen et al teach methods of tissue-specific, cell-specific and/or inducible expression of RNAi (see e.g. abstract). The invention proposes the tailoring of RNA suppression by use of

promoters that are specific to the application by limitation of the promoter to cell-specific or inducible types (see e.g. paragraph 0007-0010). RNAi molecules are transfected into cells on vectors comprising a variety of promoters including cell specific as well as CMV promoter (see e.g. table 2 and figure 6). In example 2, Allen et al demonstrate tissue specific expression of RNAi following co-transfection of RNAi and the target coding sequences each expressed using a liver specific promoter (see e.g. example 2). Furthermore, use of different promoters such as expression of the target by CMV and of the RNAi by a tissue-specific promoters demonstrated that RNAi could be used to specifically inhibit expression in the particular cell types (see paragraph 0125-0127).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express dsRNA from a vector under control of a promoter such as one that is the same or different than the target gene as taught by Allen et al to assay the effects of RNAi using alpha-complementation as taught by Michnick et al in view of Thomas et al because Allen et al teach that it is within the ordinary skill in the art to express RNAi in a tissue-specific, cell-specific or inducible manner and because Michnick et al in view of Thomas et al teach that it is within the ordinary skill of the art to assay the effect of the expression inhibiting nucleic acid using a cell-based assay comprising a fusion protein comprising ED in the presence of EA and an expression inhibiting nucleic acid. A person of skill in the art would have been motivated to express the dsRNA under control of a promoter that allows tissue specific or cell specific or inducible regulation of the RNAi for the expected benefit of limiting expression to target cells or to particular times by use of the particular promoter (see e.g. Allen et al paragraph 0007-0010). Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time

of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

January 21, 2005